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published in
Journal of Behavior Therapy and Experimental Psychiatry
2020

DOI (link to publisher)
10.1016/j.jbtep.2019.101514

document version
Publisher's PDF, also known as Version of record

Journal of Behavior Therapy and Experimental Psychiatry 66 (2020) 101514

Contents lists available at ScienceDirect

Journal of Behavior Therapy and Experimental Psychiatry

journal homepage: www.elsevier.com/locate/jbtep

Combining oxytocin and cognitive bias modification training in a randomized controlled trial: Effects on trust in maternal support

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ARTICLE INFO

Keywords:
Oxytocin
Cognitive bias modification
Trust
Attachment
Middle childhood
Randomized controlled trial

ABSTRACT

Background and objectives: Research on the social effects of intranasal oxytocin in children is scarce. Oxytocin has been proposed to have clearer beneficial effects when added to social learning paradigms. The current study tested this proposition in middle childhood by assessing effects of cognitive bias modification (CBM) training and oxytocin on trust in maternal support.
Methods: Children (N = 100, 8–12 years) were randomly assigned to one of two training conditions: CBM training aimed at increasing trust or neutral placebo training. Within each training condition, half the participants received oxytocin and half a placebo. Main and interaction effects were assessed on measures of trust-related interpretation bias and trust. We explored whether child characteristics moderated intervention effects.
Results: Children in the CBM training were faster to interpret maternal behaviour securely versus insecurely. Effects did not generalize to interpretation bias measures or trust. There were no main or interaction effects of oxytocin. Exploratory moderation analyses indicated that combining CBM training with oxytocin had less positive effects on trust for children with more internalizing problems.
Limitations: As this was the first study combining CBM and oxytocin, replication of the results is needed.
Conclusions: This study combined a social learning paradigm with oxytocin in children. CBM training was effective at an automatic level of processing. Oxytocin did not enhance CBM effects or independently exert effects. Research in larger samples specifying when oxytocin might have beneficial effects is necessary before oxytocin can be used as intervention option in children.

1. Introduction

There has been increasing interest in the therapeutic value of intranasal oxytocin administration in the early treatment of mental health disorders (DeMayo, Song, Hickie, & Guastella, 2017; Taylor, Lee, & Buisman-Pijlman, 2014). However, oxytocin studies in child populations have been scarce and sample sizes were limited. Additionally, results in both children and adults have been inconclusive and several scholars proposed that oxytocin has context-dependent effects (Bartz, Zaki, Bolger, & Ochsner, 2011; Guastella & MacLeod, 2012) and might therefore have more merit as adjunct to paradigms that employ a specific social learning context (Van IJzendoorn & Bakermans-Kranenburg, 2016). The current study was designed as a proof-of-principle test of this proposition in middle childhood, a developmental period during which children are highly susceptible to social learning (Del Giudice, 2015). The present study combines intranasal oxytocin with a cognitive

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https://doi.org/10.1016/j.jbtep.2019.101514
Received 18 May 2018; Received in revised form 3 July 2019; Accepted 22 September 2019
Available online 24 September 2019
0005-7916/

bias modification (CBM) training that previously proved effective in increasing children's trust in parental support (De Winter, Bosmans, & Salemink, 2017).

1.1. CBM training for trust

According to attachment theory, children learn to trust in their caregiver's availability and support through repeated experiences with sensitive parental responses to their needs during distress (Bowlby, 1969). Once established, trust serves as a buffer against the negative impact of stress on development throughout the lifespan (Dujardin et al., 2016). Lack of trust, however, is a transdiagnostic risk factor for the development of psychological problems (e.g., Madigan, Brumariu, Villani, Atskinson,& Lyons-Ruth, 2016). Therefore, there is need for interventions that can help promote trust in the caregiver-child relationship (e.g., Bosmans, 2016).

Trust is characterized by biases in the processing of attachment-related information (Dykas & Cassidy, 2011). For example, children with more trust interpret maternal behaviour that is ambiguous as to whether mother provides support in a more secure way, i.e., as more supportive (De Winter, Vandevivere, Waters, Braet, & Bosmans, 2016). Interestingly, accumulating research in different areas of psychology has shown, using CBM paradigms, that (interpretation) biases are not just the outcome of expectations, but can also causally affect expectations (Koster, Fox, & MacLeod, 2009). CBM procedures aim to enhance a target processing bias by systematically training participants to process information in congruence with the target bias. For disorders characterized by selective information processing biases, for example anxiety disorders, CBM procedures have been found effective in altering processing biases and reducing disorder symptoms (Hallion & Ruscio, 2011).

Applied to trust, De Winter et al. (2017) used a CBM procedure to train secure attachment-related interpretation biases and showed that this causally increased trust in maternal support. In this experiment, children were randomly assigned to CBM versus a neutral placebo training. In both conditions, children read possibly distressing scenarios in which maternal support might be needed. The CBM training taught children to systematically interpret ambiguous maternal behaviour in these scenarios in a secure manner. Two studies showed that CBM training increased speed to interpret maternal behaviour more securely, this training effect generalized to other interpretation tasks, and CBM training significantly increased trust from baseline to post-training (De Winter et al., 2017; De Winter, Salemink, & Bosmans, 2018). This suggests that training secure trust-related biases by means of a CBM training can promote trust in maternal support and such CBM procedures could therefore have therapeutic potential for interventions that target trust in parental support.

1.2. Oxytocin

However, CBM procedures only focus on the cognitive component of trust development, and neglect other factors such as the neurohormonal oxytocin system (Feldman, 2012). Apart from promoting parental care-related behaviour, oxytocin is released in individuals when they receive supportive care (Feldman, 2012; Seltzer, Ziegler, & Pollak, 2010). Prior studies manipulating oxytocin levels with a nasal spray in adults reported increased self-reported attachment security (Bernaerts et al., 2017; Buchheim et al., 2009) and trust in social interactions (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), particularly toward in-group members (De Dreu et al., 2010). Additionally, oxytocin has been proposed to enhance the salience of social stimuli (Shamay-Tsoory & Abu-Akel, 2016) and improve social information processing (Guastella & MacLeod, 2012).

The suggestion that oxytocin promotes social functioning led to the consideration of oxytocin as a treatment option for mental health disorders characterized by social functioning deficits (Bakermans-Kranenburg & Van IJzendoorn, 2013). In line with this, most child oxytocin research focused on children with autism spectrum disorder (ASD; DeMayo et al., 2017; Taylor et al., 2014). Out of five studies on children with ASD, only two found positive effects on behavioural social measures (Guastella et al., 2010; Yatawara, Einfeld, Hickie, Davenport, & Guastella, 2016). In light of these mixed results in small ASD samples, potential benefits of oxytocin on children's social functioning remain largely unclear (Taylor et al., 2014).

Specifically, the scope of oxytocin as potential therapeutic intervention goes beyond problems related to ASD (Taylor et al., 2014). Given oxytocin's effects on trust, oxytocin could have therapeutic value for interventions that target trust in parental support. However, as oxytocin has context-dependent effects (Bartz et al., 2011), it might have more clear beneficial effects when added to standardized social learning paradigms (Van IJzendoorn & Bakermans-Kranenburg, 2016), such as a CBM procedure. Moreover, the abovementioned effects of oxytocin on social information processing could enhance the processing of the socially relevant situations in the trust-related CBM training, thereby increasing CBM effects on trust. To date, however, no studies in children looked at the additive effects of oxytocin when combined with a social learning paradigm.

1.3. Present study

In the current study, children participated either in a CBM training aimed at increasing secure interpretation bias and trust, or in a neutral placebo training aimed to have no trust-related effects. Within each training condition, half of the sample received oxytocin and half received a placebo spray. Following prior studies (De Winter et al., 2017, 2018), we tested intervention effects on three outcomes. First, we tested whether the interventions affect speed of interpreting scenarios securely versus insecurely. This can be considered a direct indication of training success, measured at the most automatic level of processing. Second, we tested whether intervention effects generalize to spontaneous secure and insecure interpretation of new ambiguous maternal support-related information. Thirdly, intervention effects on expectations of trust in maternal support more generally were assessed. We predicted CBM training to increase speed to interpret ambiguous situations securely as compared to insecurely, increase secure and decrease insecure spontaneous interpretations of novel information, and increase general trust. We proposed that oxytocin could exert effects on the current study's outcomes on two levels. First, based on reported literature, oxytocin could independently positively affect the trust-related outcomes. Second, given that oxytocin can facilitate social information processing and CBM training involves the processing of social situations, we predicted oxytocin to enhance CBM effects on all three outcome levels.

Lastly, because research indicates person- and context-related moderation of oxytocin effects, we explored the moderating role of a number of child characteristics on intervention effects. Moderators were based on previous adult oxytocin research in which was found that oxytocin had more positive effects for individuals with supportive caregiving experiences (Bakermans-Kranenburg, Van IJzendoorn, Riem, Tops, & Alink, 2012; Riem et al., 2013), individuals who did not experience early adverse events (Meinlschmidt & Heim, 2007), and individuals who show impaired social functioning (Bartz et al., 2010). Additionally, oxytocin was found to have negative effects for individuals with internalizing problems (Mah, Van IJzendoorn, Smith, & Bakermans-Kranenburg, 2013). Moreover, it has been suggested that oxytocin may have more positive effects for individuals with lower endogenous oxytocin levels (Bartz et al., 2011), and individual differences in the functioning of the oxytocinergic system can be linked to biological factors such as temperament (e.g., less effortful control and more orienting sensitivity relate to higher oxytocin response;

Strathearn, Iyengar, Fonagy, & Kim, 2012), pubertal development (e.g., potential enhanced oxytocin functioning in puberty; Peper & Dahl, 2013), and duration of pregnancy (e.g., potential decreased oxytocin functioning in premature infants; Weber, Harrison, Sinnott, Shoben, & Steward, 2017). Therefore, we included caregiving/parenting, child emotional and behavioural problems, maternal separation, child temperament, pubertal development, and duration of pregnancy/birth weight as moderators. Additionally, as sino-nasal problems could impair the absorption of oxytocin (Guastella et al., 2013), we also included a measure of sino-nasal problems as potential moderator.

2. Material and methods

2.1. Participants

One hundred children (54 girls) and their mothers participated. Children were 8 through 12 years old (M_{months} = 120.42; SD_{months} = 14.42). Ninety-nine children participated with their biological mother, one with her foster mother. Most children had cohabitating parents (83%), 15% had divorced parents, one child came from a single-parent household, one lived with a foster family. For all children, mothers reported that the biological mother or both mother and father were the most prominent caregivers during their first year of life. Regarding maternal and paternal educational level, 8% and 17% had a high school degree, 39% and 27% had a post high-school technical training or bachelor degree, and 53% and 48% had a master's degree, respectively. Eight percent of the data regarding father's educational level was missing.

2.2. Study design and procedure

The study was a double-blind randomized controlled trial with a 2x2 factorial design, resulting in four conditions with 25 participants per condition: 1) CBM training and oxytocin; 2) CBM training and placebo; 3) Neutral training and oxytocin; and 4) Neutral training and placebo. Randomization of the nasal sprays was carried out at the University Hospital of Heidelberg, Germany. Nasal spray randomization was stratified by training condition and performed as permuted block randomization. Nasal sprays were numbered and assigned to consecutive participants in sequential order, with training condition alternated between participants. Participants were blind to their intervention condition. Experimenters were aware of training but blind to nasal spray condition. Blinding was maintained until data collection was finished. The study took place at KU Leuven, Belgium between March and November 2016. The Medical Ethics Committee UZ KU Leuven/Research approved the study. The trial was registered in the database of ClinicalTrials.gov (NCT02737254).

Participants were recruited via flyer distribution. Inclusion criteria were: 8–12 years old, able to comprehend and read the Dutch language. Exclusion criteria were: a known oxytocin allergy, current medication use, a kidney or cardiac condition. One hundred fifty-four parent-child dyads initially stated interest in the study, of which 64.9% participated (see Fig. 1). Upon arrival at the laboratory, mother and child completed written informed consent and assent respectively. The child's procedure entailed: (1) baseline trust questionnaire, (2) baseline recognition task, (3) (oxytocin or placebo) nasal spray administration, (4) 35-min break, (5) (CBM or neutral) training, (6) post-intervention recognition task, (7) post-intervention trust questionnaire, (8) side-effects questionnaire. An additional mother-child interaction task was administered, but not discussed here. The child's procedure lasted approximately 120 min (M = 123.89; SD = 13.12). Meanwhile, mother completed questionnaires in a different room. Full details of the study methods and procedure are available in the published study protocol (Verhees et al., 2017).

2.3. Interventions

2.3.1. Nasal spray

Half of the participants received oxytocin (in a concentration of 40 international units(IU)/ml), the other half received placebo (0.9% sodium-chloride solution). The bottles containing oxytocin and placebo were identical. Following prior child oxytocin research (Dadds et al., 2014), we used a weight-based dosing strategy: children under 40 kg administered 0.3 ml nasal spray (12 IU oxytocin for the oxytocin condition), children over 40 kg administered 0.6 ml (24 IU oxytocin). No differential side effects of oxytocin versus placebo were found in the current study (Verhees et al., 2018).

2.3.2. Training

Children read 30 short scenarios, divided over 6 blocks, which described possibly distressing situations. In the last line of the scenarios a word was missing, rendering the outcome of the scenario unclear. On the next screen, the missing word was presented as an incomplete word fragment that children had to resolve by pressing the missing letter on the keyboard as soon as possible.

In the CBM training, the scenario outcome was always ambiguous as to whether mother provided support, and children were trained to interpret ambiguous maternal behaviour as supportive (Fig. 2). In the neutral training, the scenario outcome was always unrelated to maternal support (Fig. 2). This way, the neutral training should not influence children's interpretation of mother's behaviour. Further details about the format and content of the scenarios can be found in (Verhees et al., 2017) and De Winter et al. (2017). Based on previous studies' effects sizes (De Winter et al., 2017, 2018), the current sample size yielded a power of 0.83 to detect medium effects of CBM training on trust.

2.4. Measures

2.4.1. Outcome measures

2.4.1.1. Interpretation speed of secure and insecure scenario resolutions. Besides the training scenarios, each training block contained two probe scenarios that were the same for CBM and neutral training. One of these probes always had a secure resolution (mother provided support), the other always had an insecure resolution (mother did not provide support). Reaction times (RTs) to word fragments following the probes were used to test differences in interpretation speed of secure versus insecure resolutions between conditions (De Winter et al., 2017). RTs to probes that were not correctly resolved were excluded from analyses (7.2% of the trials; there were no effects of spray, training or spray by training on the number of errors children made on the probe scenarios, Fs between 0.10 and 3.09, $ps > .08$). Additionally, for each probe, RTs deviating more than 3SDs from the participants' mean RT to that probe were excluded (1.7% of the trials). Mean RTs to secure and insecure resolving word fragments were analysed separately.

2.4.1.2. Change in spontaneous secure and insecure interpretation of ambiguous maternal behaviour. Children's spontaneous interpretation of ambiguous maternal behaviour was measured with a recognition task at baseline and post-intervention (De Winter et al., 2017). Children read seven scenarios describing possibly distressing situations which remained ambiguous as to whether mother provided support. For two events per scenario (one secure event describing supportive maternal behaviour and one insecure event describing unsupportive maternal behaviour) children rated to what extent they thought the event transpired in the scenario on a scale ranging from 1 (completely untrue) to 4 (completely true). As none of the described events actually occurred in the scenarios, the scores reflect children's spontaneous interpretation of ambiguous maternal behaviour. Change in secure and insecure interpretations was examined by calculating

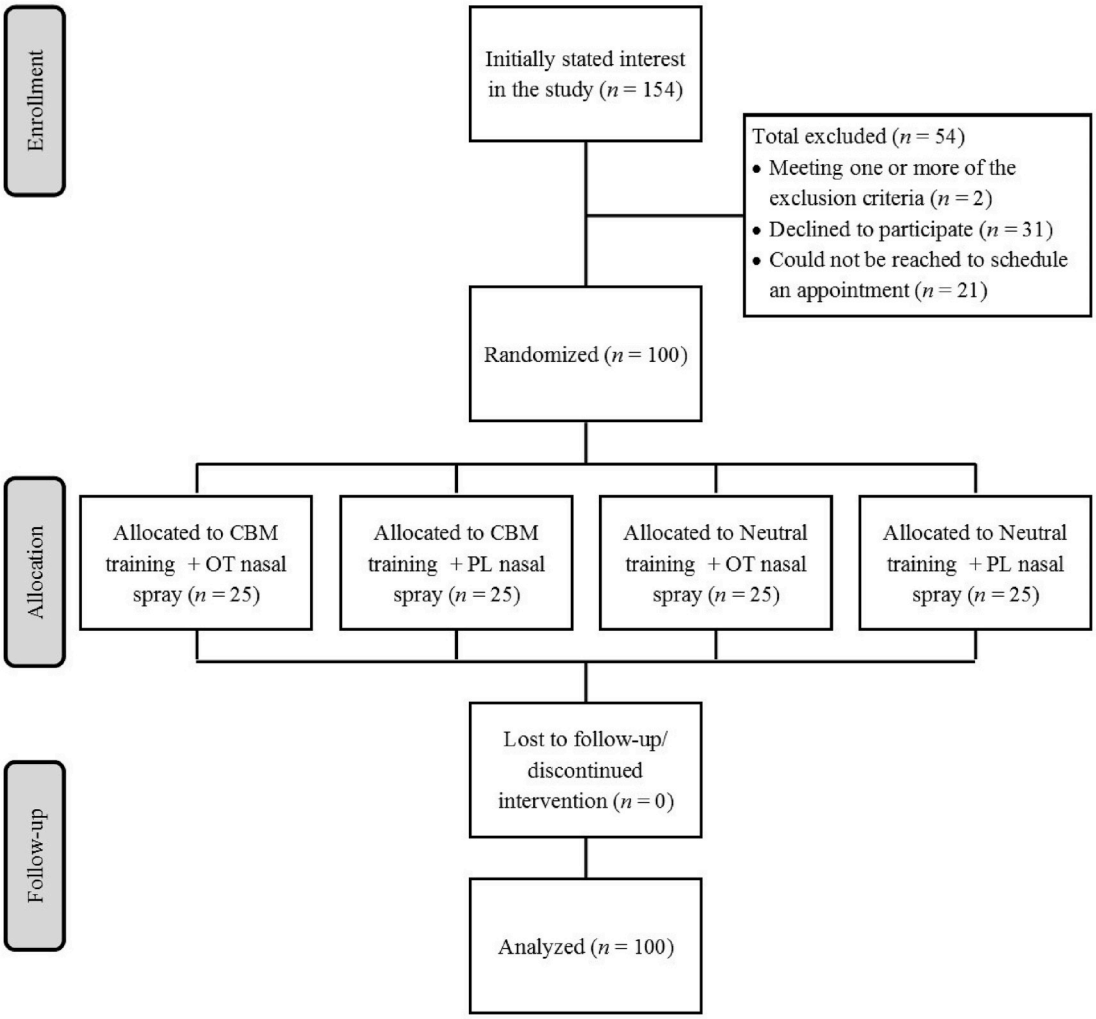

Fig. 1. Consort flow diagram. CBM = cognitive bias modification; OT = oxytocin; PL = placebo.

difference scores between baseline and post-intervention for secure and insecure interpretations separately.

2.4.1.3. Self-reported trust. At baseline and post-intervention, trust in mother was assessed with the Trust subscale of the People In My Life Questionnaire (PIML; Ridenour, Greenberg, & Cook, 2006). This subscale contains 10 items concerning experiences with mother as a trustworthy source for support (e.g. 'I can count on my mother to help me when I have a problem'). Children rated the items on a scale from 1 (almost never true) to 4 (almost always true). Cronbach's *α*s were 0.77 and 0.82 for the baseline and post-intervention trust subscales respectively. Difference scores were calculated that directly represented change in trust from baseline to post-intervention.

2.4.2. Other measures

2.4.2.1. Mood. Children rated their mood at baseline and post-intervention on two Visual Analogue Scales: one assessed how happy children felt, the other how sad they felt.

2.4.2.2. Background questionnaires. Mothers provided background information by completing questionnaires. A demographic questionnaire inquired about children's demographic characteristics. The Early Adolescent Temperament Questionnaire-Revised (EATQ-R; Ellis & Rothbart, 2001) measured children's temperament on four factors (Oldehinkel, Hartman, De Winter, Veenstra, & Ormel, 2004): Effortful control (18 items, $\alpha = 0.87$), Surgency (14 items, $\alpha = 0.83$), Negative affect (12 items, $\alpha = 0.82$), and Affiliation (6 items, $\alpha = 0.71$) and social-emotional functioning on two behavioural scales: Aggression (6 items, $\alpha = 0.73$) and Depressive mood (5 items, $\alpha = 0.84$). The Child Behaviour Checklist (CBCL; Achenbach, 1991) assessed children's Internalizing problems (32 items, $\alpha = 0.87$) and Externalizing problems (35 items, $\alpha = 0.86$). The Pubertal Developmental Scale (PDS; Petersen, Crockett, Richards, & Boxer, 1988) assessed children's pubertal status. One item ('His/her growth spurt') was left out of the analyses since 17% of the mothers were unsure whether this started yet. Cronbach's α for the remaining four items was 0.84. The brief Sino-Nasal Outcome Test (SNOT-20; 10 items, $\alpha = 0.75$; Piccirillo, Merritt, & Richards, 2002) assessed children's recent sino-nasal problem symptoms. Two questionnaires measured mother's self-perceived parenting. The short Ghent Parental Behaviour Scale (GPBS; Van Leeuwen & Vermulst, 2010) assessed Supportive parenting (13 items, $\alpha = 0.82$) and Negative control (9 items, $\alpha = 0.72$). A second questionnaire comprised three subscales: Responsiveness of the Louvain Adolescent Perceived Parenting Scale (LAPPS; 7 items, $\alpha = 0.71$; Delhaye, Beyers, Klimstra, Linkowski, & Goossens, 2012), Autonomy support (Perceptions of Parents Scale; Grolnick, Ryan, & Deci, 1991), Psychological control (Psychological Control Scale; Barber, 1996). The latter two subscales were not used in further analyses because of low Cronbach's *α*s (0.57 and 0.55 respectively).

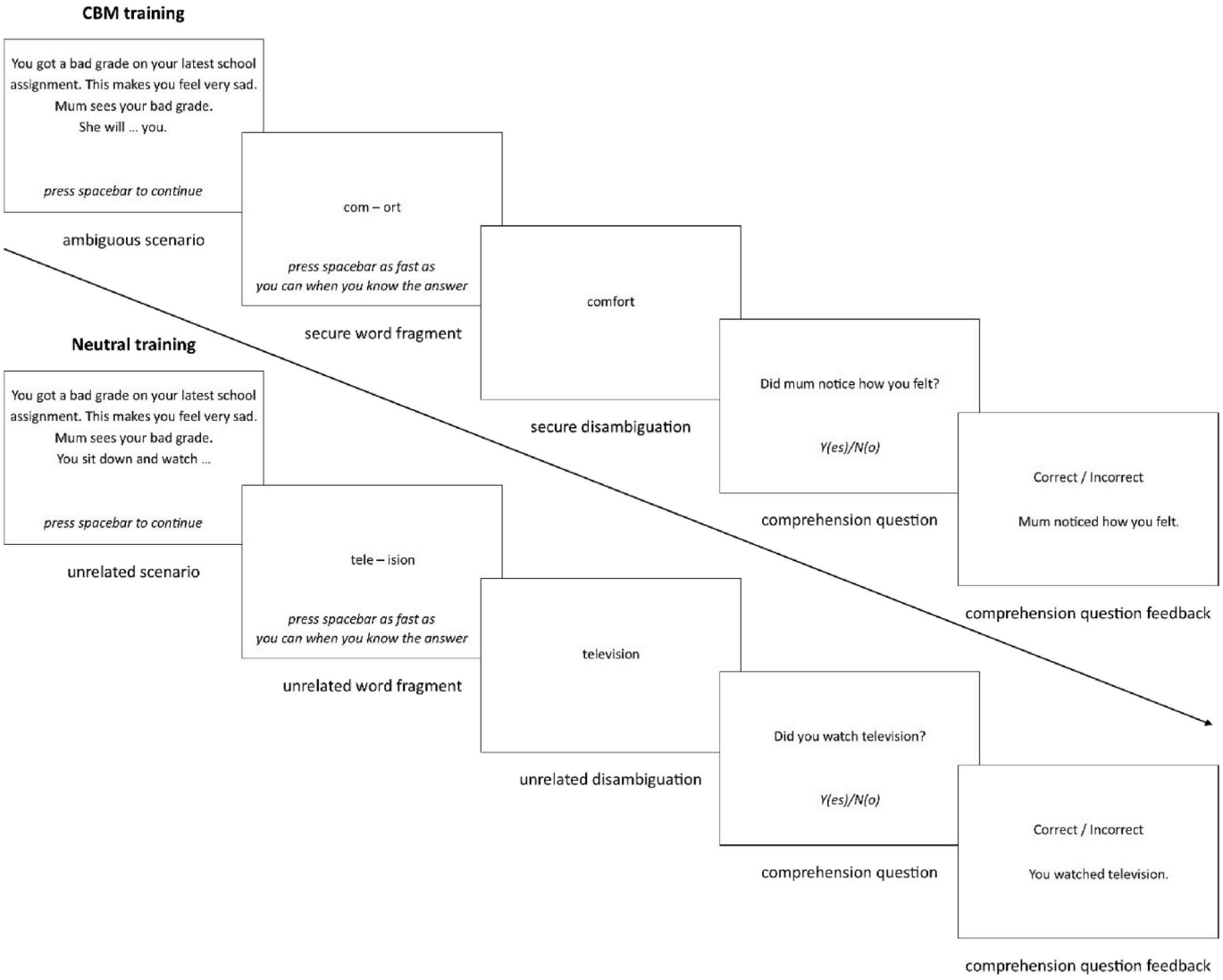

Fig. 2. Overview of a CBM training scenario and a neutral training scenario.

3. Results

3.1. Preliminary analyses

Of the data, 0.11% was missing completely at random (Little's MCAR test $\chi^2(1176) = 0.00$, $p = 1.00$). Missing data were imputed using Expectation Maximization. There were no significant differences in distribution of gender across conditions ($\chi^2(3) = 7.25$, $p = .06$) and controlling for gender did not affect the results in terms of direction or significance. Age did not differ across conditions ($F(3,96) = 1.87$, $p = .14$). Procedural factors, i.e., time of testing, procedure duration and nasal spray dose,[1] did not differ across conditions (Fs between 0.14 and 1.33, ps $> .27$). Table 1 reports the child descriptives per condition. Mood did not change as a function of condition ($F_{positive\ mood}(3,96) = 0.08$, $p = .97$; $F_{negative\ mood}(3,96) = 0.77$, $p = .51$). There were no significant differences among conditions on baseline Interpretation bias scores (ps $> .07$) and Trust ($p = .66$).

3.2. Outcome measures

Table 2 reports the values of the outcome variables per condition.

3.2.1. Interpretation speed of secure and insecure scenario resolutions

A mixed ANOVA with training (CBM versus neutral) and spray (oxytocin versus placebo) as between subject factors and probe valence (secure versus insecure) as within-subject factor indicated a significant training by valence interaction on RTs to probe scenarios ($F(1,96) = 7.01$, $p < .01$, $\eta_p^2 = 0.07$). Paired-samples t-tests revealed that participants in the CBM training responded significantly faster to secure probes than insecure probes ($t(49) = 7.87$, $p < .001$, Cohen's $d = 0.90$) as compared to participants in the neutral training ($t(49) = 3.00$, $p < .01$, $d = 0.38$). There was no nasal spray by valence interaction ($F(1,96) = 0.07$, $p = .79$, $\eta_p^2 = 0.00$), nor a training by nasal spray by valence interaction ($F(1,96) = 1.31$, $p = .26$, $\eta_p^2 = 0.01$) on RTs.

3.2.2. Secure and insecure interpretation of ambiguous maternal behaviour

For secure interpretations there was a main effect of time across conditions ($t(99) = 2.49$, $p < .02$), indicating a decrease in secure interpretations from baseline to post-intervention. A two-way ANOVA

[1] We planned to check whether oxytocin dose affected intervention effects on the outcome measures. However, as only 7 children in the oxytocin condition weighted over 40 kg and thus received the higher dose of 24 IU oxytocin, too small and unequal groups prohibited such analysis. Adding the procedural factors nasal spray dose, time of testing and procedure duration as covariates in the main analyses did not change the results in terms of direction or significance.

Table 1
Child descriptives per condition.

	CBM + OT	CBM + PL	Neu + OT	Neu + PL
Gender				
Boy	8	10	17	11
Girl	17	15	8	14
Age in months, *M (SD)*	122.36 (13.15)	121.28 (14.76)	114.72 (14.60)	123.32 (14.29)
Weight				
< 40 kg	21	21	22	20
> 40 kg	4	4	3	5
Start time of testing				
9 a.m.–11 a.m.	7	9	9	8
12 noon-14 p.m.	7	2	11	10
14 p.m.–16 p.m.	11	14	5	7
Family situation				
Cohabitating parents	19	24	19	21
Divorced parents	6	1	5	3
One-parent household	0	0	1	0
Foster family	0	0	0	1
Family income				
< €1500	0	0	0	0
€1500-€2250	2	0	2	0
€2250-€3000	2	2	3	3
€3000-€4500	12	12	13	13
> €4500	9	11	7	9
Pubertal development, *M (SD)*[a]	0.14 (0.91)	0.10 (1.06)	−0.38 (0.20)	0.14 (1.39)
Maternal separation, *M (SD)*[a]	−0.17 (0.70)	0.10 (1.15)	−0.03 (0.96)	0.10 (1.15)
Sino-nasal problems, *M (SD)*[a]	−0.06 (0.92)	−0.04 (1.00)	0.13 (1.12)	−0.04 (1.00)
Birth weight/length of pregnancy, *M (SD)*[a]	0.14 (0.96)	−0.20 (1.37)	0.21 (0.63)	−0.15 (0.90)
Temperament, *M (SD)*[a]	0.11 (1.29)	0.05 (1.00)	0.06 (0.87)	−0.21 (0.79)
Internalizing problems, *M (SD)*[a]	−0.19 (1.08)	−0.15 (0.82)	0.01 (1.02)	0.32 (1.04)
Externalizing problems, *M (SD)*[a]	−0.38 (0.86)	−0.14 (1.12)	0.34 (1.04)	0.18 (0.86)
Responsive and supportive parenting, *M (SD)*[a]	0.24 (0.94)	0.00 (0.97)	0.03 (1.02)	−0.26 (1.06)
Negative controlling parenting, *M (SD)*[a]	−0.06 (0.95)	−0.09 (1.10)	−0.03 (1.09)	0.18 (0.88)

Note. CBM = cognitive bias modification; Neu = neutral training; OT = oxytocin; PL = placebo.
[a] *z*-score.

Table 2
Values of the outcome variables per condition.

	Reaction times (ms)		Secure interpretations		Insecure interpretations		Trust	
	Secure probes	Insecure probes	Baseline	Post-intervention	Baseline	Post-intervention	Baseline	Post-intervention
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
CBM + OT	2839 (1176)	3857 (1557)	3.26 (0.47)	3.25 (0.42)	1.87 (0.54)	1.87 (0.47)	3.59 (0.38)	3.59 (0.42)
CBM + PL	2470 (992)	3827 (1507)	3.31 (0.47)	3.35 (0.29)	1.74 (0.48)	1.91 (0.48)	3.60 (0.36)	3.68 (0.34)
Neu + OT	3638 (1476)	4297 (1288)	3.35 (0.51)	2.95 (0.40)	1.81 (0.57)	2.07 (0.53)	3.69 (0.22)	3.72 (0.27)
Neu + PL	3294 (1447)	3744 (1526)	3.33 (0.42)	3.19 (0.40)	2.14 (0.65)	2.19 (0.60)	3.65 (0.26)	3.70 (0.25)

Note. CBM = cognitive bias modification; Neu = neutral training; OT = oxytocin; PL = placebo.

with training and spray as between-subject factors indicated a significant training effect ($F(1,96) = 8.34$, $p < .01$, $\eta_p^2 = 0.08$). Follow-up paired-samples t-tests revealed that in the neutral training, participants' secure interpretations decreased ($t(49) = 4.50$, $p < .001$, $d = 0.60$), whereas in the CBM training participants' secure interpretations remained stable ($t(49) = -0.18$, $p = .86$, $d = 0.03$). There was no main effect of nasal spray ($F(1,96) = 2.56$, $p = .11$, $\eta_p^2 = 0.03$), nor an interaction effect of training by nasal spray ($F(1,96) = 1.12$, $p = .29$, $\eta_p^2 = 0.01$) for secure interpretations.

For insecure interpretations there was a main effect of time across conditions ($t(99) = -2.09$, $p < .04$) indicating an increase in insecure interpretations from baseline to post-intervention. A two-way ANOVA with training and spray as between-subject factors indicated no effects of training ($F(1,96) = 0.35$, $p = .56$, $\eta_p^2 = 0.00$), nasal spray ($F(1,96) = 0.04$, $p = .85$, $\eta_p^2 = 0.00$) nor the interaction between training and nasal spray ($F(1,96) = 2.61$, $p = .13$, $\eta_p^2 = 0.03$).

[2] Holding the moderator variables constant, i.e., adding them as covariates in the analyses, did not change the results in terms of direction or significance.

3.2.3. Trust

Across all four conditions there was a main effect of time on trust, indicating an increase in trust from baseline to post-intervention ($t(99) = -2.19$, $p < .04$). A two-way ANOVA with training and spray as between-subject factors indicated no effects of training ($F(1,96) = 0.00$, $p = 1.00$, $\eta_p^2 = 0.00$), nasal spray ($F(1,96) = 1.72$, $p = .19$, $\eta_p^2 = 0.02$), nor the interaction between training and nasal spray ($F(1,96) = 0.76$, $p = .38$, $\eta_p^2 = 0.01$) on change in self-reported trust.

3.3. Exploratory moderation analyses

To explore whether participant characteristics might have affected intervention effects, moderation analyses were performed based on the mother-reported questionnaires. Change in trust was the outcome measure for these analyses as this was the study's primary dependent variable of interest. Three different scale/item scores were tested as separate moderators: pubertal development (PDS); maternal separation; and sino-nasal problems (SNOT-20). Moreover, five other concepts that were measured by multiple scales or questionnaires were defined and

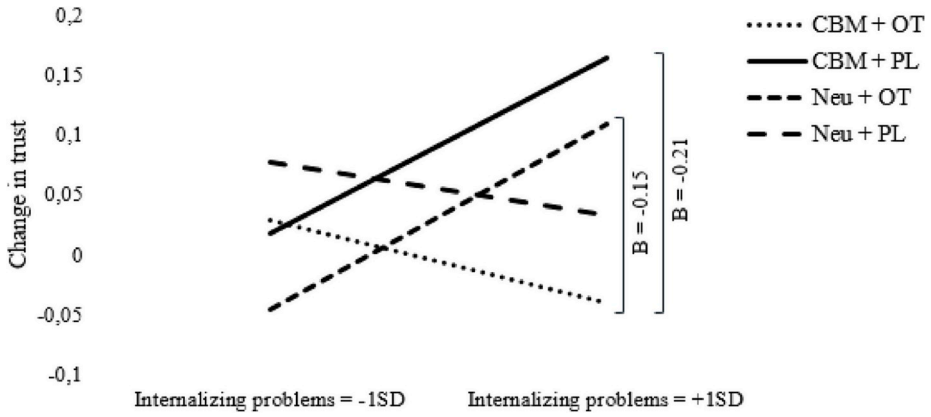

Fig. 3. Relationship between internalizing problems and change in trust for the four intervention conditions. CBM = cognitive bias modification; Neu = neutral training; OT = oxytocin; PL = placebo.

factor analyses were performed to check whether these scales could be integrated in one factor. Five factors were distinguished with eigenvalues of at least one and item/scale loadings of at least 0.39: birth weight/length of pregnancy; temperament (EATQ-R temperament scales); internalizing problems (CBCL Internalizing/EATQ-R Depressive mood); externalizing problems (CBCL Externalizing/EATQ-R Aggression); and responsive and supportive parenting (LAPPS Responsiveness/GPBS Supportive parenting). The scale of negative controlling parenting (GPBS Negative control) was tested as a separate moderator since the factor analysis loadings revealed that this scale could not be integrated in a general parenting factor together with responsive and supportive parenting. Of these moderators, only the factor internalizing problems ($t = -2.77$, $p < .007$, $f^2 = 0.09$) interacted with training and nasal spray on change in trust. However, after Bonferroni correction for multiple testing ($p < .05/9 = 0.006$), the interaction was only marginally significant.[2]

PROCESS (Hayes, 2013) was used to further examine this interaction. To test from which value on the interaction became significant, we used the Johnson-Neyman technique and found that for children who scored ≥ 0.41 on internalizing problems (28% of the sample) the interaction between training and nasal spray was significant. For these children, the interaction reflected that the combination of CBM and oxytocin had a less positive effect on change in trust than only CBM (combined with placebo): $t = -2.49$, $p < .02$; and only oxytocin (combined with neutral training): $t = -2.03$, $p < .05$ (see Fig. 3).[3]

4. Discussion

The current study was designed to assess whether oxytocin could have beneficial effects on trust in middle childhood independently and as adjunct to social learning focused paradigms. Therefore, oxytocin administration was combined with a previously effective CBM training to assess their effects on three outcomes related to trust in maternal support. Importantly, results showed that children in the CBM training responded faster to secure probe scenarios versus insecure probes as compared to children in the neutral training. This indicated that the CBM training was effective in enhancing secure interpretation bias at the most automatic level of processing. Similar effects were found in prior studies using the same CBM procedure (De Winter et al., 2017, 2018). In the present study, oxytocin per se or in combination with training did not affect interpretation speed of secure versus insecure probes.

Contrary to previous studies, in the present study CBM effects did not generalize to children's spontaneous interpretations of ambiguous maternal behaviour. Secure interpretations of ambiguous scenarios remained stable after CBM training, whereas they decreased after neutral training. Training did not affect insecure interpretations of ambiguous scenarios. There were no main or interaction effects of oxytocin on secure and insecure interpretation of ambiguous maternal behaviour. Additionally, no main or interaction effects of CBM and oxytocin on expectations of trust in maternal support were found.

The finding that oxytocin did not significantly affect the present study's outcomes could raise the question whether oxytocin administration was effective in elevating oxytocin levels in relevant brain regions. Indeed, controversy exists about optimal dosing and delivery strategies (DeMayo et al., 2017). In the current study, most children received 12 IU oxytocin because they weighed under 40 kg. This dose is relatively low in comparison with adult studies in which typically 24 IU oxytocin is administered. The low dose may be one reason why no clear effects of oxytocin were obtained in the present study. Nevertheless, adding weight and nasal spray dose as covariates in the main analyses did not change the results in terms of significance or direction. Moreover, to date it is unclear how exactly intranasal oxytocin reaches the brain to exert its effects, how it interacts with other neuropeptides such as vasopressin (Van IJzendoorn & Bakermans-Kranenburg, 2016), and how a potential diurnal rhythm of endogenous oxytocin may influence effects of intranasal oxytocin administration. A better understanding of these factors could facilitate the interpretation of (lack of) intranasal oxytocin results. In the current study, we did test whether nasal obstruction resulting from rhinitis influenced the results and this factor did not appear to have suppressed potential oxytocin effects.

The finding that CBM training effects did not generalize beyond interpretation speed of secure versus insecure scenarios, was unexpected as previous studies using the same CBM procedure did find positive effects on secure and insecure interpretation of ambiguous maternal behaviour and on trust (De Winter et al., 2017, 2018). One could therefore question the strength of the CBM effects on the more generalized trust measures in the present study. On the one hand, CBM may not have exerted effects on trust in the current sample, for example because children in the current study differed from those in previous CBM studies. Specifically, one concern could be that children in the current sample already scored high on baseline trust, which might have limited the possibility to increase trust in the present study as compared to previous CBM studies. However, this explanation seems unlikely since the sample in De Winter et al. (2017) was selected to represent a securely attached sample and scored significantly higher on baseline trust than the current sample. Additionally, there were no significant

[3] Because the exploratory moderation analyses pointed to internalizing problems as moderator of the intervention effects on trust, we conducted an additional analysis with current mood as moderator. To this aim, a factor score was calculated based on children's baseline mood ratings ($VAS_{positive\ mood}$/$VAS_{negative\ mood}$). The analysis revealed that children's mood at baseline was not a significant moderator of intervention effects on trust ($t = -0.20$, $p = .84$).

differences on baseline trust and recognition task scores between the current sample and the sample of De Winter et al. (2018). Nonetheless, to further explore the proposition that baseline trust affected intervention effects, we performed three post-hoc moderation analyses with baseline scores of trust, secure interpretation bias, and insecure interpretation bias as moderators of the intervention effects on change in trust. These baseline measures did not significantly moderate the intervention effects across all four conditions (t between -0.19 and -1.85, p between .07 and .85), nor did they significantly relate to change in trust when tested per condition (r between -0.37 and 0.15, p between .07 and .91).

On the other hand, the change in procedure with the addition of oxytocin to the CBM training may have reduced training effects. We discuss two possible explanations for this proposition. First, expectancy effects following the administration of a nasal spray may have masked generalized effects of CBM training on trust. That is, across all four conditions trust in maternal support increased from baseline to post-intervention. The finding of a placebo response is not uncommon in clinical trials, especially in child samples (Yatawara et al., 2016). Additionally, adjunctive treatment and low baseline severity (participants did not score low on baseline trust) can stimulate placebo response (Masi, Lampit, Glozier, Hickie, & Guastella, 2015). It is interesting to note that the participants' belief about which interventions they received did not moderate intervention effects on trust ($t = 0.85$, $p = .39$). However, as placebo effects occur even without concealment or deception (Kaptchuk et al., 2010), we cannot rule out the option that placebo effects might have at least partly compromised the study results.

Second, while oxytocin did not have any main or interaction effects on the outcome measures, the exploratory moderation analyses suggest that oxytocin might have had differential effects for different children. Important for the current purposes, for children with relatively high levels of internalizing problems, the combination of oxytocin and CBM seemed to have a less positive effect on trust than the interventions separately. For this subgroup, the addition of oxytocin to CBM may have suppressed effects of CBM on generalized trust-related bias and self-reported trust, but because the interaction did not survive correction for multiple testing this interpretation should be considered preliminary. Previous studies already reported differential effects following intranasal oxytocin in depressed adult women (e.g. Mah et al., 2013). However, in the current study, specifically the combination of oxytocin and CBM seems to have exerted less positive effects in children high(er) on internalizing problems. It has been suggested that oxytocin effects depend on the degree to which social stimuli are relevant and salient, and that oxytocin can enhance the processing of both positive and negative social stimuli (Shamay-Tsoory & Abu-Akel, 2016; Van IJzendoorn & Bakermans-Kranenburg, 2016). Therefore, a cautious and speculative explanation of the less positive effect of the CBM and oxytocin combination on trust could be that oxytocin enhanced the processing of the insecure probe scenarios, specifically in combination with CBM training and for children high(er) on internalizing problems. Insecure probes might have been more salient in the CBM condition because they deviated more from the default secure training and probe scenarios than in the neutral training condition in which the majority of the scenarios was neutral instead of secure. The more a specific stimulus deviates from the average stimuli, the more likely it is that the deviant information is processed (Wagemans et al., 2012), and this effect could have been enhanced by oxytocin. Additionally, children high(er) on internalizing problems may already have been more susceptible to negative, insecure scenarios. So, it might have been that these children, after the administration of oxytocin, were more susceptible to potential negative effects of the discrepant insecure probes in the CBM training. However, lack of power makes it difficult to draw conclusions from the current moderation analyses and future studies in larger and more diverse samples are clearly needed to allow a more reliable examination of potential moderators of the current intervention effects. Moreover, the current study only represented a preliminary test of some of the factors that may moderate intervention effects, and thus several other relevant moderators, for example autistic traits and anxious attachment (Bartz et al., 2011), remain untested in the present study. Therefore, future research may want to consider other potential moderators.

In addition, these post-hoc explanations for the current findings are tentative and future research is needed to see whether the pattern of results replicates in other samples. It remains possible that other factors than the addition of oxytocin could explain the absence of CBM effects on trust in the present study, and that the role of oxytocin in enhancing CBM effects was compromised as CBM training overall was not clearly effective. Therefore, future research assessing the effects of oxytocin as adjunct to social learning paradigms should include a different paradigm than CBM training to see whether the current results replicate. If the current findings replicate, this would call for a further investigation of the mechanisms underlying the interplay between oxytocin and social learning.

5. Conclusion

Despite the current study's limitations, the current findings are important in light of the consideration of oxytocin as addendum to social learning paradigms. Based on the present findings we can cautiously conclude that oxytocin is not a catalyst of the previously reported positive effects of CBM, as no generalized CBM effects were found in the present study. The results further suggest that even when the learning context is standardized, comprises social stimuli, and previously exerted positive effects, for children with certain characteristics the addition of oxytocin might even have iatrogenic effects. While the current study was performed in a community sample, these results indicate that caution is warranted in the clinical use of oxytocin for childhood populations. In line with adult studies reporting context-dependent oxytocin effects, the current results suggest that also for children the therapeutic potential of oxytocin should be considered in the context of patient characteristics and adjunctive treatments. Further research specifying parameters for if and when oxytocin might have beneficial effects is clearly needed before oxytocin can be used as an intervention option with children.

Acknowledgements

This work was supported by grants G.0774.15 and G.0757.18 from Research Foundation Flanders (FWO) and CREA/12/004 from Research Fund KU Leuven. MJBK was supported by an Advanced Grant from the European Research Council. The authors declare that they have no competing interests.

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